Comparison of Single Monthly Instillations of Intra-Vesical Bacillus Calmette-Guerin Maintenance Therapy with Southwest Oncology Group Regimen in Non-Muscle Invasive Bladder Cancer Patients- A Retrospective Analysis In a Single Institute

Alireza lashay[1], Saeed Taleghani[2], Navid Masoumi[1]*

Purpose: To compare the efficacy and complication rate of monthly instillations of Bacillus Calmette-Guerin (BCG) as maintenance therapy in intermediate and high risk Non-Muscle Invasive Bladder Cancer (NMIBC) patients with the current standard Southwest Oncology Group (SWOG) protocol.

Materials and Methods: In this observational retrospective study, 40 intermediate and high risk NMIBC patients, receiving standard BCG maintenance regimen, were compared with another 40 NMIBC patients, undergoing monthly intra-vesical instillations of BCG with regard to recurrence, progression and major and minor adverse effects.

Results: The two groups were similar in their basic characteristics except for the older age in the monthly instillation group (70.95 ± 9.66 years vs. 64 ± 8.8, $p = 0.001$). Study objectives between the monthly instillation group and the standard group, including recurrence (17.5 % vs. 25%, $p = 0.34$) and progression rate (7.5% vs. 10%, $p = 0.54$) did not show statistically significant difference. Major and minor complication rate also did not show any difference between the two groups.

Conclusion: In addition to the currently recommended standard protocol of BCG maintenance therapy, our study shows that the monthly regimen can be recommended in intermediate and high risk NMIBC patients without compromising the efficacy of the treatment.

Keywords: adverse effects; BCG immunotherapy; maintenance schedule; progression; recurrence

INTRODUCTION

One to 3 years of intra-vesical Bacillus Calmette-Guerin (BCG) maintenance therapy is the recommended regimen in intermediate and high risk Non-Muscle Invasive Bladder Cancer (NMIBC) patients after resection of visible tumors and induction course of BCG[1,2]. However, the optimal dose and the frequency of its instillation are not clearly defined[1]. The most applied protocol for maintenance BCG is based on the Southwest Oncology Group (SWOG) trial by Lamm et al.[3] in which maintenance BCG is administered in 3 weekly doses at the 3rd and 6th months following Transurethral Resection of Bladder Tumor (TURBT) and 3 weekly repetitions every 6 months up to 3 years.

Although this regimen is considered as the gold standard, it is only an empirical program based on weak clinical evidence and other alternative protocols have also been suggested; i.e. monthly instillations[4-6], 3 monthly instillations for 1 year[7], 6 doses of BCG every 6 months for 2 years[8], or single instillation every 6 months for 3 years[9], but the studies that compare these regimens in an head-to-head manner is rather scarce.

With this state in mind, we designed the current retrospective study to compare the SWOG regimen with our method of monthly instillations in efficacy and complications rate.

MATERIALS AND METHODS

Patients selection

All NMIBC patients who underwent tumor resection from April 2015 to study commencement at our institution were considered for this retrospective observational institutional review board approved study. They were chosen from the patients of the two attending urologists in one university hospital whom met our study's criteria. The inclusion criteria were patients in whom, after tumor resection and induction course of BCG, there was no residual cancer at 3 months follow up cystoscopy and were candidate to commence maintenance therapy. Patients who had serious side effects to the induction course which dissuaded commencing maintenance therapy were not included in the analysis. Lost to follow up patients or participants with missed records were also excluded. In the end, a total of 80 patients who had complete and valid follow up records were selected for comparison (**Figure 1**). All persons gave us their informed consent.

Each of the attending urologists practices different regimens of BCG maintenance (classic SWOG or monthly instillation) as their accepted approach and based on that, we had two groups of patients' records; Group 1, from patients' records of the 1st attending which received classic SWOG protocol, and Group 2 from patients' records of the 2nd attending which received

[1]Department of urology, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran/Iran.
[2]Urology Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran/Iran.
*Correspondence: Saadat Abad St., Shahid Modarres Hospital, Tehran/Iran
Cell phone: +989123084965. Tel: +982122074087. Fax: +982122074101. Email: nmasoumig@gmail.com.
Received September 2020 & Accepted May 2021

Table 1. Baseline characteristics of the patients in the two groups

Characteristics		Group 1 †(n=40)	Group 2 ‡(n=40)	*P* value
Age (years)		64 ± 8.84	70.95 ± 9.66	0.001
Gender (%)	Male	35 (87.5)	33 (82.5)	0.5
	Female	5 (12.5)	7 (17.5)	
Smoking History (%)	Yes	38 (95)	36 (90)	0.6
	No	2 (50)	4 (10)	
Cancer Stage(%)	Carcinoma In Situ	0 (0)	2 (5)	0.3
	T1	26 (65)	21(52.5)	
	Ta	14 (35)	17 (42.5)	
Cancer Grade(%)	High Grade	28 (70)	27 (67.5)	0.8
	Low Grade	12 (30)	13 (32.5)	

†Group 1: Standard SWOG protocol
‡ Group 2: Monthly BCG instillation group

monthly BCG instillations (40 patients in each group). Each patient had been briefed about the regimen and after consent, had been commenced with the maintenance protocol.

Maintenance schedule

Four weeks after tumor resection, all patients received 120 mg of intra-vesical BCG (Mycobacterium Bovis, Pastor 1173P2 strain, 5-30 $\times 10^6$ CFU/vial, PASTOCIS®, Pastor Institute, Iran, Tehran) for 6 consecutive weeks as induction phase. A check cystoscopy was done 6 weeks after induction phase, and patients with no tumor were considered for maintenance therapy.

The length of therapy (1 or 3 years) had been chosen based on the NMIBC risk group (intermediate or high risk). Risk stratification was based on the model outlined by 2016 AUA/SUO guideline and European Organization for Research and Treatment of Cancer trials (EORTC) risk tables of recurrence and progression, presented by Sylvester et al[10]. As mentioned, the patients had been assigned into two groups based on the treating physician's policy. No tumor or patient characteristics had been considered in group assignments of the participants. In both groups the follow up protocol for cancer recurrence was the same, including urine cytology and cystoscopy every 3 months for 1 year, every 6 months for the next 2 years, and annually afterwards, with inclusion of upper urinary tract imaging in case of new onset hematuria.

In case of severe irritative voiding symptoms, hematuria or symptoms lasting more than 48 hours, the dose was reduced to half in the next instillations.

Our primary outcome variable was to compare the ef-

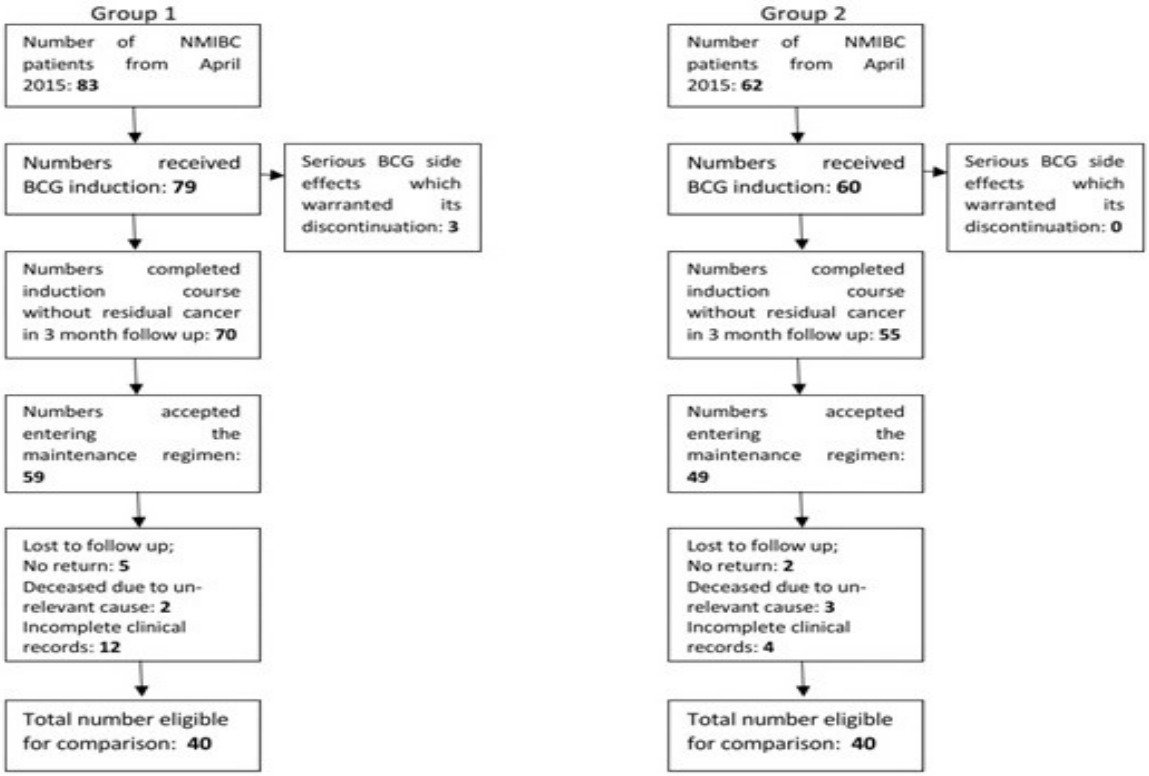

Figure1: Flow diagram of patient selection in accordance to our study criteria.
Group 1: Group receiving SWOG protocol, Group 2: Group receiving monthly BCG

Table 2. Number of patients having BCG complications in the two groups

Variable	Group 1†(n=40)	Group 2‡(n=40)	*P* value
Minor Complications (%)	32(80)	30(75)	0.2
Major Complications (%)	2(5)	0(0)	

†Group 1: Standard SWOG protocol
‡ Group 2: Monthly BCG instillation group

ficacy, i.e. reduction of recurrence and progression of NMIBC lesions, of monthly BCG in relation to SWOG regimen. The secondary outcome variable was the difference of adverse events between the two groups. Recurrence was defined as the appearance of bladder lesions of the same characteristics to the primary lesion during follow up. This also included any lesions of lower stage or grade. Progression was defined as the appearance of bladder lesions of higher stage or grade than primary lesions during follow up. BCG side effects entailed minor (dysuria, frequency, hematuria and urgency) and major symptoms (high grade fever, systemic symptoms, generalized weakness and pulmonary or hepatic complications).
In case of recurrence or BCG side effects which forces discontinuation of treatment, the duration of follow up was defined until the time of recurrence or occurrence of side effects. In those who completed the maintenance regimen, the time of the last cystoscopy was defined as the end of follow up.

Statistical analysis

We used SPSS V.22 program for statistical calculations. Mean value was used for description of qualitative parameters. Chi square test and Fisher's exact test were used for difference analysis of quantitative variables between the two groups. *P* value < 0.05 was considered significant.

RESULTS

The participants' characteristics are summarized in Table 1. Other than mean age which was higher in group 2 (70.95 ± 9.66 years Vs. 64 ± 8.86, $p = 0.00$), the two groups were comparable in other properties.
Group 1 received 7.5± 2.72 and group 2 received 7.28 ± 3.46 doses of maintenance BCG (p= 0.74). With inclusion of induction course, group 1 and group 2 received a total sum of 13.5 ± 2.72 and 13.27 ± 3.46 doses, $p = 0.74$, respectively. The average time of follow up was 36.68 ± 17.37 months in group 1 and 33.45 ± 17.35 months in group 2 ($p = 0.4$).
Table 2 demonstrates the BCG complication rate. Despite the prevalence of minor complications in the two groups (80% in group 1 and 75% in group 2, $p = 0.2$), patients in group 2 did not experience any major complications. In two patients in group 1, BCG maintenance was discontinued due to fever, weakness and severe anhedonia. No difference was observed between the two groups in regard to minor or major complication rate.
Table 3 summarizes the recurrence and progression rate. There was no statistically significant difference in the rate of recurrence [Group1: 10 out of 40 (25%)), Group 2:(7 out of 40 (17.5%)), $p = 0.34$] and progression [Group1: 4 out of 40 (10%), Group2: 3 out of 40 (7.5%), $p = 0.54$)] between the two groups.

DISCUSSION

There is a general consensus in prescribing BCG maintenance therapy in patients responsive to induction course[1,2], however the issue of proper dose and timing continues to remain an area of contention due to the dearth of studies in this area. Meanwhile, reducing adverse effects and improving patients' compliance by incorporating feasible schedules have always been a concern which have been addressed in several studies [4,5,9].
The pivotal study by Lamm et. al. demonstrated that the maintenance regimen of 3 weekly instillations at 3 and 6 months after induction course with 6 monthly repetitions for 3 years, not only decreased the recurrence rate, but also decreased progression and metastases rate which ended up in improved overall survival[3].
With the scope of maintaining efficacy while decreasing BCG complications by the way of reducing the number of maintenance instillations, the Spanish Urology Association for Oncological Treatment (CUETO) group[9], conducted an experiment with 3 monthly instillations of single dose of BCG for 3 years, for a total sum of 12 instillations and compared them with another group which did not receive maintenance regimen. Their trial demonstrated no difference between the 2 groups in regard to recurrence rate. They concluded that 3 monthly instillations are not enough to boost immunity against cancer cells and postpone recurrence and recommended designing a study with 2 doses of 3 monthly instillations for 3 years with the end of reaching SWOG regimen's efficacy as well as dose reduction.
With the above mentioned goal in mind, multiple BCG instillation regimens was proposed in other trials[4,5,7,8,11]. Akaza et.al. study[4] on 107 bladder cancer patients, showed that monthly BCG instillations did not decrease the recurrence and progression rate in compar-

Table 3. Number of patients having recurrence and progression in the two groups

Variable	Group 1† (n=40)	Group 2‡ (n=40)	*P* value
Recurrence (%)	5(12.5)	7(17.5)	0.5
Progression (%)	4(10)	3(7.5)	1.0

†Group 1: Standard SWOG protocol
‡ Group 2: Monthly BCG instillation group

ison to the classic method. However, their result cannot be generalized because of two reasons. First, they used 40 mg (half dose) of Tokyo 172 variant and second, this study was the phase 2 of another study in which the patients received BCG in lieu of tumor resection and in those whom no response were observed, maintenance BCG was started. This treatment plan is not the standard approach nowadays and complete tumor resection of visible lesions is a must before considering BCG treatment.

Other trial by Badalomente et. al.[5] on 93 patients for comparison of monthly instillations of BCG with no instillations, also did not reveal any advantage of monthly instillations on reducing recurrence or progression.

Yoo et. al.[11] studied the role of monthly BCG in 92 patients with NMIBC and compared them with 34 patients on no maintenance regimen with regard to Recurrence Free Survival (RFS) , Progression Free Survival (PFS) , Disease Specific Survival (DSS) and side effects. The median follow up time was 43 months. They reported that the monthly regimen resulted in improved RFS. The estimated median RFS was 87 months (95% CI 53.0-120.9) in the maintenance group and 48 months (95% CI 0-96.8) in the no maintenance group (P = 0.002). They also reported that the toxicity and side effects were higher in the no maintenance group by 4% which was not statistically significant. Again, this study did not compare the monthly regimen with the classic SWOG regimen, but only compared them with no maintenance regimen which obviously result in better recurrence results. Furthermore, although the side effects were higher in the no maintenance group, all of their symptoms were minor irritative symptoms. While in the maintenance group, major side effects including gross hematuria, high grade fever and pulmonary tuberculosis were occurred.

Single instillation of BCG every 3 months for 1-year (4 doses total) which was adopted in another trial[7] did not show any results either which was no surprise considering the results of CUETO[9] study which had already showed 3 monthly single injections will not suffice to harness efficacy. Six instillations every 6 months for 2 years adopted by Palou[8] as maintenance protocol also did not result in any difference in recurrence or progression rate, in comparison to control group (no maintenance instillations).

In our retrospective study, we demonstrated that monthly BCG maintenance instillations can provide similar efficacy to SWOG regimen with no additional complication rate. Also the advanced age in group 2 did not cause any difference in efficacy or complication rate in comparison to group 1.

The only study which had compared monthly BCG with SWOG protocol in an head-to-head manner is the prospective trial conducted by Gupta N.K. et al,[6] in 2020. In their trial, 78 intermediate and high risk BCG naive NMIBC patients were randomized into 2 groups of monthly BCG or SWOG protocol. Monthly group received 12 monthly doses of 80 mg Moscow strain BCG and the other group received BCG in accordance with the SWOG regimen of 80 mg BCG for 3 consecutive weeks at 3 and 6 months and 6 monthly thereafter for a period of 3 years. Their mean follow-up was 24 months (range: 15-31). The rate of recurrence, progression and BCG toxicity were statistically insignificant between the two groups and they concluded that SWOG protocol can be replaced by monthly regimen in NMIBC.

Our results are in line with Gupta's trial[6]. In the SWOG maintenance group (Group 1) 12.5 % of patients had recurrence at the end of follow up (15% in Gupta's trial (6) at the end of 2 years) and in the monthly group (Group 2) 17.5 % of patients had recurrence at the end of follow up (16.1 % in Gupta's trial[6] at the end of 2 years). Our follow up time was longer (36.68 ± 17.37 months in group 1 and 33.45 ± 17.35 months in group 2) and still monthly regimen proved to be effective. Another difference was that in Gupta's trial[6] all patients in SWOG group received BCG for 3 years and in monthly group for 12 months, irrespective of their risk group (intermediate or high), however in our study, intermediate risk patients received BCG for 1 year and high risk patients received BCG for 3 years.

Regarding BCG major complications, the reason for its absence in our study, could be due to the fact that any major complications commonly do occur in the induction course[12]. Since we excluded these patients from study, there is no surprise that we had low major complication rate, and we can deduct that patients who do not show serious complications for induction course, will tolerate maintenance dose as well. This finding is also in line with Gupta's trial[6] in which both groups only demonstrated grade 1 level of BCG toxicity (i.e. minor) and grade 2 and 3 (i.e. major) were absent.

Our monthly regimen did not decrease the total number of instilled BCG (36 versus 21 in SWOG regimen, if 3 years of maintenance is completed), however since it disperses the instillation times, it is probably a more convenient schedule for patients which could increase their compliance. The issue of compliance has always been a concern in long term BCG maintenance therapy, as in the SWOG trial[3], only 16% of patients had completed the treatment. In Gupta's study[6] the dropout rate was 7.3% for monthly group while it was 18.4% for the SWOG group. Although the difference was not statistically significant, they hypothesized from their patients' given reasons that adopting treatment at short orderly intervals was easier to follow.

There is a theory regarding monthly BCG instillation that with monthly boost, there is the possibility of keeping the immunity more on edge[13,14]. This raises the question of "If monthly BCG instillation keeps the immunity more alert, is it possible to decrease the amount of prescribed dosage or even the total maintenance time to derive the same efficacy?". Obviously, this statement is just theoretical and needs a larger trial for verification.

This was a retrospective study with its inherent limitations. Furthermore, the number of patients was limited and it requires a larger population to derive extensible results. The reason for our results could be due to patient selection bias. All our patients had good response to induction course, were free of tumor in their follow up cystoscopy, had good compliance and had no serious complications with instillation. Good response to induction course could translate into BCG sensitivity of these patients[15,16]. Still, this will not compromise the validity of our study because our objective was to compare two different regimens and this can be done in primary BCG responsive patients.

CONCLUSIONS

In the aggregate, after induction course, our regimen of

monthly instillations of BCG as maintenance therapy, shows no difference in the complication rate in comparison to SWOG protocol and it has comparable efficacy regarding recurrence and progression rate.

CONFLICT OF INTEREST

None was declared by the authors.

REFERENCES

1. Babjuk M, Burger M, Compérat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol. 2019;76:639-57.
2. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016;196:1021-9.
3. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:1124-9.
4. Akaza H, Hinotsu S, Aso Y, Kakizoe T, Koiso K. Bacillus Calmette-Guérin treatment of existing papillary bladder cancer and carcinoma in situ of the bladder. Four-year results. The Bladder Cancer BCG Study Group. Cancer. 1995;75:552-9.
5. Badalament RA, Herr HW, Wong GY, et al. A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. J Clin Oncol. 1987;5:441-9.
6. Gupta N, Sarkar D, Pal D. Monthly maintenance protocol Bacillus Calmette–Guerin as a viable alternative to Southwest Oncology Group maintenance protocol in nonmuscle-invasive bladder cancer: A prospective randomized study. Urology Annals. 2020;12:116-21.
7. Koga H, Ozono S, Tsushima T, et al. Maintenance intravesical bacillus Calmette-Guérin instillation for Ta, T1 cancer and carcinoma in situ of the bladder: randomized controlled trial by the BCG Tokyo Strain Study Group. Int J Urol. 2010;17:759-66.
8. Palou J, Laguna P, Millán-Rodríguez F, Hall RR, Salvador-Bayarri J, Vicente-Rodríguez J. Control group and maintenance treatment with bacillus Calmette-Guerin for carcinoma in situ and/or high grade bladder tumors. J Urol. 2001;165:1488-91.
9. Martínez-Piñeiro L, Portillo JA, Fernández JM, et al. Maintenance Therapy with 3-monthly Bacillus Calmette-Guérin for 3 Years is Not Superior to Standard Induction Therapy in High-risk Non-muscle-invasive Urothelial Bladder Carcinoma: Final Results of Randomised CUETO Study 98013. Eur Urol. 2015;68:256-62.
10. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-5; discussion 75-7.
11. Yoo KH, Lim TJ, Chang SG. Monthly intravesical bacillus Calmette-Guérin maintenance therapy for non-muscle-invasive bladder cancer: 10-year experience in a single institute. Exp Ther Med. 2012;3:221-5.
12. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013;63:462-72.
13. de Reijke TM, de Boer EC, Kurth KH, Schamhart DH. Urinary cytokines during intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer: processing, stability and prognostic value. J Urol. 1996;155:477-82.
14. Ratliff T, Catalona W. Depressed proliferative responses in patients treated with 12 weeks of intravesical BCG. J. Urol. 1989;141:230A.
15. Chen S, Zhang N, Shao J, Wang X. Maintenance versus non-maintenance intravesical Bacillus Calmette-Guerin instillation for non-muscle invasive bladder cancer: A systematic review and meta-analysis of randomized clinical trials. Int J Surg. 2018;52:248-57.
16. Woldu SL, Bagrodia A, Lotan Y. Guideline of guidelines: non-muscle-invasive bladder cancer. BJU Int. 2017;119:371-80.